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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,815	06/06/2002	Takehiko Koide	06478.1461	2579

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EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,815	KOIDE, TAKEHIKO	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 2-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 2-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The examiner acknowledges Amendment and Response under 37C.F.R. § 1.111 filed on August 28, 2003. Amendments have been entered as requested. Claim 1 is cancelled. Claims 2-6 are amended; new claims 7-9 are added. Claim 2-9 are pending and are the subject of this Office Action.

DETAILED ACTION

1. Objections

Objection to the specification made in the previous Office Action is withdrawn because the specification has been amended.

2. Rejections

2.1. 35 USC, section 112, first paragraph

2.1.1. Lack of written description

Claim 2-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The reasons are stated in the previous Office Action, Paper No. 10 and reiterated herein.

The claims are directed to a human antithrombin variant characterized in that at least one of the amino acids at positions 78, 278, 378 and 380 are changed. The claims are directed to a large genus of human antithrombin variants, but the specification fails to describe its structure. No single representative species of the genus is disclosed by presenting its amino acid sequence and its sequence identification number; neither the encoding gene of the polypeptide is given. Therefore,

one skilled in the art does not know what amino acid sequence is to be modified so that its amino acids in positions 78, 278, 378 and 380 are substituted.

Federal Circuit states that the primary function of the written description requirement is to insure that an inventor had possession of the claimed subject matter and to allow one skilled in the art to recognize what is claimed. *See in re Blaser*, 556F.2d 534, 194 U.S. P. Q. 122(CCPA 1977), *Enzo Biochem*, 285 F. 3d 1013, 62 U.S.P.Q.2d 1289. The written description requirement is satisfied by the disclosure of the claimed subject matter in such a descriptive means, *e.g.*, words, structures, figures and diagrams, to allow one skilled in the art to visualize or recognize the claimed subject matter, *Enzo Biochem.* 285 F. 3d 1013."

One skilled in the art is not able to visualize or recognize the invention because the claimed subject matter is not disclosed in such descriptive means as structures, or figures presenting such structures or even words presenting details of structures claimed. Because the specification completely lacks the amino acid and nucleotide sequence that are to be mutated to obtained the claimed invention, one skilled in the relevant art concludes that the inventor(s), at the time the application was filed, had no possession of the claimed invention.

In their Remarks in their response Applicants assures that because the specification identifies natural antithrombin III as the protein to be modified and the protein sequence of natural antithrombin III is well known in the art, the amino acid sequence to be modified should not be identified by its sequence identification number.

Applicants' arguments have been fully considered but are found not persuasive. Even if the specification identifies human natural thrombin III as the protein to be modified, human antithrombin III has been known at the time of filing of the instant application to have several forms. For example, "Aalborg" and "Budapest" antithrombins III have been well known natural variants (see the PTO 892 form and enclosed copies of articles). Therefore, as long as the sequence of antithrombin III used for modification is not taught by the specification and/or recited in the claims, the claims are rejected for lack of written description.

3.2.2. Lack of enablement

Rejection of claims 1-6 made in the previous Office action paper No.10 is moot in case of canceled claim 1, and withdrawn in case of claims 2-6 because Applicants arguments are found persuasive.

3.3. 35 USC section 102

Rejection of claim 1 under 35 U.S.C. 102(b) as being anticipated by Huntington J. A. et al. (Conformational Conversion of Antithrombin to a Fully Activated Substrate of Factor Xa without Need for Heparin, *Biochemistry* 1998, 37, 3272-3277) is moot because the claim has been cancelled.

Rejection of Claim 6 under 35 U.S.C. 102(b) as being anticipated by Huntington J. A. et al. (Conformational Conversion of Antithrombin to a Fully Activated Substrate of

Factor Xa without Need for Heparin, *Biochemistry* 1998, 37, 3272-3277) is withdrawn, because the claim has been amended.

3.4. 35 USC section 103

Claims 5 and newly filed claim 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huntington J. A. et al. (Mechanism of Heparin Activation of Antithrombin. Evidence for Reactive Center Loop Preinsertion with Expulsion upon Heparin Binding, *Biochemistry*, 1996, 35, 8495-8503, and Conformational Conversion of Antithrombin to a Fully Activated Substrate of Factor Xa without Need for Heparin, *Biochemistry* 1998, 37, 3272-3277) in view of common knowledge in molecular biology, for the reasons indicated in the previous Office Action, paper No. 10. The rejection is reiterated herein.

Huntington et al. generated, by site directed mutagenesis, a variant of antithrombin wherein serine in position 380 is substituted by thryptophan (1996) or cysteine (1998); see the abstracts of both papers. The variants do not require heparin activation for its inhibitory function. Huntington et al. do not teach substitution of residue 380 by other amino acids like alanine, aspartic acid, glycine, histidine, ileucine, leucine, asparagines, threonine, tyrosine, and valine. However, it would have been obvious to one having ordinary skill in the art at the time of invention to have antithrombin and modify it to heparin independence by substituting the residue 380 by amino acid other than tryptophan and cysteine, similarily as Huntington et al.did..

The motivation is provided by Huntington et al. who write, "This accounts both for the occurrence of thrombosis in patients whose antithrombin has a defect in heparin binding or activation and for the widespread clinical use of exogenous heparin as anticoagulant" (page 3272 of the 1998 paper, left column, line 20). Thus, one skilled in the art would be motivated to obtain antithrombin that is more clinically useful by making it independent on its activator, heparin by mutatin position 380 using several amino acids, and screening for the mutants having required property of heparin independence. The expectation of success was very high, because Huntington et al. teach that position 380, having functional symbol P14, needs to be displaced from beta-sheet A of the protein to render it heparin independent (page 3272 of 1998 paper, right column, line 33.). The displacement can be achieved by substitution of serine 380 by other amino acid.

In their response Applicants, on page 7, line 16 write, "In his 1996 paper, Hantington states that the inhibitory action of antitrombin III is 'very sensitive to the correct folding of antithrombin." Based on this fact, Applicants conclude "Any mechanism that exhibits a high level of structural sensitivity is likely going to be similarly sensitive to changes to its structure. Accordingly, a person skilled in the art would know that substituting alternate amino acids into known functional sites of anithrombin III would not necessarily by successful" (page 7, line 20).

Applicants' argument has been fully considered, but is found not persuasive for the following reasons. Although substituting position 380 in anthithrombin III by any of about 20 amino acids of which the protein is build may not lead to a heparin

independent antithrombin, **Hantington et al. have shown that the probability of success is high**, because they were successful in two of about 20 cases, which is about 20%. Applicants results confirm that the probability of success was high because they succeeded in obtaining mutants with desired property using further 10 of about 20 amino acids, i.e. probability of success is actually higher than about 50%.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

5. Conclusion

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Patent Examiner

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